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RADIUM

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VOL. XII DECEMBER, 1918 No. 3

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A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES

RADIUM

A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY, PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES

Edited and Published by Charles H. Viol, Ph. D., and William H. Cameron, M. D. with the assistance of collaborators working in the fields of Radiochemistry, Radioactivity and Radiumtherapy.

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VOL. XII DECEMBER, 1918 No. 3

OBSERVATIONS ON THE TREATMENT OF MYELOCYTIC LEUKEMIA BY RADIUM*

By Herbert Z. Giffin, M.D., Rochester, Minn.

Renon, Degrais and their associates (1910) were the first to treat myelocytic leukemia by means of radium exposures over the enlarged spleen. In 1913 they reported five cases. In the first case satisfactory remissions were obtained with five series of exposures over a period of two years. Death occurred two years and two months after the first treatment. In the case of their second patient, a satisfactory result was obtained over a period of nine months with two series of exposures. Death occurred twelve months after the first treatment. Two patients were in good condition six months after their first treatment. The fifth patient had been splenectomized prior to the use of radium, a 2800 gm. spleen having been removed. Following the splenectomy, the leukocytes fell to 27,000, but subsequently rose to 143,000. Benzol was used without apparent effect. The asplenic area was then exposed to radium, and this procedure was curiously followed by a reduction of the leukocytes to 21,500. It was not noted by the authors that the reduction may have been a late effect of benzol; it may, on the other hand, have been due to the direct effect of radium on the large amount of blood in the abdominal cavity. Radium was next applied over the thighs, but the leukocytes rose to 81,600. Radium had been applied over the thighs in one other case of this series without favorable result.

Renon and Degrais mentioned that twelve patients had been treated by other French observers with the initiation of favorable remissions.

In the English literature a few cases have been reported in which radium exposures were followed by remissions. Similar results have

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been obtained by Peabody and by Burnam in this country in a large series of unpublished cases.

In May, 1916, before the Association of American Physicians, Ordway* presented a complete and instructive discussion concerning radium therapy in myelocytic leukemia, and placed on record a detailed study of one of his cases in which a remarkable remission had been brought about by means of radium emanations. In this case the patient had been formerly resistant to both the roentgen ray and benzol. Death occurred, however, fifteen months after the recognition of the disease.

The results of these various observers lead only to the conclusion that it is important to make use of this method of treatment, when possible, in order to initiate a remission in a disease with so unfavorable a prognosis. Our own experience from May 15, 1916, to April 1, 1917, comprises a series of thirty consecutive cases of myelocytic leukemia which have been treated by means of the surface application of radium element over the spleen.

Method of Application. In some instances in this series we used 50 mg., and in others 100 mg. of the radium element in tubes. The enlarged spleen was mapped out into squares in the manner described by Ordway, and the radium exposed over each area for periods of three or four hours. The total length of time for each series of applications varied from twelve to forty-eight hours; usually, however, the time was from twenty-four to thirty-six hours. Patients remained in bed during exposure. In the early cases the protection consisted only of 2 mm. of lead beneath the radium and 2 mm. of lead over the radium. The radium was held in place by means of adhesive plaster. Superficial burns resulted, but they were never serious and healed without difficulty. As previously pointed out by Ordway, our experiences demonstrated that the skin formerly traumatized by adhesive plaster was especially susceptible to burn. After adding ½ inch of wood beneath the 2 mm. lead screen we obtained results equally satisfactory, with only occasionally a slight burn. The radium may be raised so far from the skin by means of gauze that little result is obtained from the exposures. When a satisfactory response does not occur we reduce the protection, even to the point of burning the patient. Dr. W. J. Tucker, working with me, devised a biscuit-shaped block which has been used routinely for several months. This consists of ½ inch of wood, 2 mm. of lead, ½ inch of wood bored to receive the tubes of radium, and above this 2 mm. of lead and another ½ inch of wood. The block is held in position by means of a simple canvas belt. An endeavor is made to concentrate the fire through the most massive portions of the spleen.

Clinical Experience. For convenience of presentation, our thirty cases have been classified with respect to the size of the spleen at the time of the original examination. The degree of splenic enlargement is denoted by the Scale 1-4. Scale 4 represents a spleen of enormous size, extending beyond the midline and into the right iliac fossa, practically filling the abdomen; Scale 3, a spleen the edge of which extends well to the right of the navel; Scale 2, a spleen extending beyond a point midway between the costal edge and the umbilicus; and Scale 1, a spleen which is easily palpable or which extends only a couple of inches from the costal edge. Spleens having unusual contour or position have been represented by their approximate equivalents in this scale.

There were four patients with spleens in the Scale 1 group (small but easily palpable spleens). The spleen was reduced to approximately

*Reprinted in Radium, X, 1-16, October 1917. Ed.

normal size in these four patients in from thirty-nine to sixty-one days, after from 2000 to 6600 mg. hours of radium given in from two to five series of exposures. The leukocytes in one instance fell from 207,000 to 12,800 in forty days, and in another from 97,000 to 6600 in thirty-nine days. The general condition and the anemia in all these patients were definitely improved.

TABLE I

MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

SPLEEN—SCALE 1. (SLIGHTLY ENLARGED.)

Number	Previous Leukocyte Count	Previous Neut. Myelocyte Percentage	Subsequent Leukocyte Count	Subsequent Neut. Myelocyte Percentage	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
173,312	12,200	11.0	3,800	1.7	1 to normal	46 days	5,400	4
175,574	97,000	19.0	6,600	1.0	1 to normal	39 days	3,800	2
186,558	207,000	27.7	12,800	8.3	1 to normal	40 days	6,600	5
169,876	96,000	20.7	8,400	2.7	1 to normal	61 days	2,000	2

TABLE II

MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

SPLEEN—SCALE 2. (MODERATELY ENLARGED.)

Number	Previous Leukocyte Count	Previous Neut. Myelocyte Percentage	Subsequent Leukocyte Count	Subsequent Neut. Myelocyte Percentage	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
160,937	188,000	28.0	9,400	0	2 to normal	50 days	2,600	2
	107,600	18.7	68,000	18.3	1 to normal	20 days	800	1
159,989	329,000	29.7	7,000	2.3	2 to normal	54 days	4,300	2
	62,000	14.3	15,800	3.3	1 to normal	31 days	4,450	3
181,494	125,600	7.3	3,800	.3	2 to normal	70 days	5,400	5
183,015	229,000	19.0	81,800	11.3	2 to 1	21 days	5,350	4
187,921	8,200	4.7	6,200	1.7	2 to 1	11 days	3,600	2
172,156	389,000	47.0	147,000	33.3	2 to 1+	13 days	2,000	2
	343,000	25.3	42,600	9.3	2 to 1	23 days	7,000	4
173,445	214,000	29.0	22,000	8.0	2 to 1+	48 days	5,400	3

There were 7 patients with spleens in the Scale 2 group (spleens extending nearly or quite to the region and level of the navel). In 3 of the 7 the spleen was reduced to approximately normal size in from fifty to seventy days after from 2600 to 5400 mg. hours of radium, given in from two to five series of exposures. Two of these patients were discharged at the end of fifty and fifty-four days from the time of the first exposures, their leukocyte counts having fallen from 188,000 to 9400 and from 329,000 to 7000. They returned in four months and in two months, respectively, with leukocytic counts of 107,600 and 62,000 and their spleens slightly enlarged. Reduction again occurred to approximately normal size in twenty and thirty-one days, respectively, with, in one instance, one series of exposures, and in the other, three. The patients were in such good general condition that it was thought inadvis-

able to extend the treatment to the point of reducing the leukocytes to a normal count. As has been stated, 3 of the 7 patients in this group were discharged with approximately normal size spleens. In the remaining 4 the spleens were reduced to Scale 1.

In one case (187921) the diagnosis was somewhat doubtful. The history was satisfactory for myelocytic leukemia, but the leukocyte count was in the neighborhood of 8000 cells, of which 4.7% were myelocytes. It is quite probable, however, that the case will prove itself to be one of myelocytic leukemia.

In another case of this group, one of long standing (172156), the improvement in the general condition was not commensurate with the reduction in the size of the spleen and the leukocyte count.

TABLE III

MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

SPLEEN—SCALE 3. (MARKEDLY ENLARGED.)

Number	Previous Leukocyte Count	Previous Neut. Myelocyte Percentage	Subsequent Leukocyte Count	Subsequent Neut. Myelocyte Percentage	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
173,772	360,000	29.3	5,800	.7	3 to 1	69 days	8,000	5
177,183	712,000	39.7	18,200	6.7	3+ to 1	122 days	9,400	6
183,919	24,300	12.7	16,000	20.3	3 to 1	41 days	5,800	5
188,262	222,000	22.3	22,000	9.3	3 to 1	22 days	9,000	3
170,257	389,000	40.3	20,900	21.7	3 to ?	10 days	1,800	1
168,142	88,000	50.7	34,600	27.3	3 to 2	12 days	3,150	2
169,360	142,000	40.3	9,800	9.3	3+ to 2	43 days	3,600	2
173,740	29,000	20.3	15,200	19.3	3+ to 2	7 days	1,400	1
173,747	8,200	15.7	1,600	2.3	3 to 2	98 days	3,400	3
181,399	395,000	32.7	19,000	0	3 to 2	41 days	7,750	8
52,388	258,000	32.7	108,000	27.0	3+ to 3	12 days	4,450	2

There were 11 patients with spleens in the Scale 3 group (very large spleens, extending well beyond the level of the navel). Four of the 11 spleens were reduced to Scale 1, or were easily palpable in from twenty-two to one hundred twenty-two days after from 5800 to 9400 mg. hours in from three to six series of exposures. Six of the 11 spleens were reduced to Scale 2, or extended approximately midway between the costal edge and the navel. In one, there was only a slight reduction. This patient, however, was in very poor physical condition and treatment was not continued.

One patient of Scale 3 group (173747) gave a satisfactory history for leukemia, but the leukocyte count was low—8200 with 15.7% myelocytes. The leukocyte count became reduced, after three series of exposures, to 1600 cells, of which 2.3% were myelocytes; the size of the spleen was little changed. In the series as a whole, an extreme leukopenia, such as occurred in this case, has been guarded against. The patient began to show changes in the mechanism of coagulation, and slight epistaxis occurred. Transfusion was done and he improved immediately. Three months later he had a definite leukocytosis, which further corroborated the diagnosis. Another patient of this group (169360) showed a marked hemorrhagic tendency, at the time of the first examination, *i.e.*, epistaxis, hematuria, petechial and purpuric eruptions, and a very toxic condition. After two series of exposures, a total of 3600

mg. hours, over a period of forty-three days, all hemorrhage ceased, the patient's general condition improved remarkably, the leukocytes were reduced from 142,000 to 9800, and the spleen was considerably smaller. It has been repeatedly noted following radium treatment that the hemorrhages cease when the condition of the patient becomes improved. A very rapid improvement and reduction of the leukocyte count occurred in one patient (170257), in whom, after one series of exposures, 1800 mg. hours, the leukocyte count became reduced in ten days from 389,000 to 29,900.

TABLE IV

MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

SPLEEN—SCALE 4. (HUGE.)

Number	Previous Leukocyte Count	Previous Neut. Myelocyte Percentage	Subsequent Leukocyte Count	Subsequent Neut. Myelocyte Percentage	Reduction in Size of Spleen	Time Between Counts	Mg. Hours	Number of Treatments
175,791	918,000	25.7	19,600	13.0	4 to 1	31 days	8,300	5
162,899	280,000	28.0	11,600	0	4 to 2	57 days	5,300	3
178,536	773,000	35.0	25,000	3.7	4 to 1	75 days	7,700	5
180,499	604,000	28.3	5,600	.7	4 to 1	46 days	10,000	6
176,684	215,000	16.3	8,200	4.3	4 to 1	26 days	4,600	3
168,742	16,400	17.0	4,200	4.3	4 to 2	33 days	4,500	1
175,480	470,000	33.3	157,000	10.3	4 to 3	105 days	7,550	7
166,824	644,000	43.0	30,400	34.7	4 to 3	99 days	4,350	3

There were 8 patients with spleens in the Scale 4 group (enormous spleens). The most remarkable results were seen in some of the cases of this group. In 4 of the 8 patients, the spleen became reduced from Scale 4 to Scale 1 in from twenty-six to seventy-five days after from three to six series of exposures, totaling from 4600 to 10,000 mg. hours. In the remaining 4 cases there was a very considerable reduction in the size of the spleen and in the leukocyte count, in spite of the fact that 2 of the patients were *in extremis,* and no results would ordinarily have been expected from treatment. In one instance in this group the leukocyte count was reduced from 918,000 to 19,600 in thirty-one days after five series of exposures. In another instance the leukocyte count was reduced from 773,000 to 25,000 in seventy-five days after five series of exposures. In this latter patient the reduction of the spleen was remarkable.

Another patient of this group (168742) presented a satisfactory history for leukemia, while the leukocyte count was only 16,400, of which 17% were myelocytes. It is apparently not of rare occurrence to observe in myelocytic leukemia a huge spleen without extreme leukocytosis, the case being of more chronic type with longer history; this type of case is apt to show a less marked remission as the result of radium treatment.

It is not possible, without extended discussion, to follow in detail the individual cases of the series; however, the temporary effect of the treatment by radium exposures has been demonstrated. The ultimate results cannot be summarized at this time, but there is no reason to believe that the effect will be other than temporary. In 14 of the 30 cases, after a marked reduction of the size of the spleen had been brought about by means of radium, splenectomy was done without opera-

tive mortality. The postoperative course of these cases cannot be satisfactorily discussed at present.

The Differential Count. The reduction, not only of the absolute number, but also of the relative percentage of myelocytes, is most striking after radium treatment. As a less extreme and quite representative example, one instance (168742) may be cited in which the myelocytes fell from 29.7% of 329,000 cells to 2.3% of 7000 cells, or from approximately 98,000 cells to 140 cells. It has always been possible to find myelocytes in the smears, on prolonged search, though they have occasionally been absent on the routine differential count.

The reduction of the number of neutrophilic polynuclears is also striking. The relative percentage remains approximately the same before and after treatment. But the reduction of the absolute polynuclear count is very great; for example, in the case previously cited, a reduction from 57% of 329,000 cells to 70.7% of 7000 cells, or from approximately 187,000 cells to 5000 cells.

Although the relative percentage of small lymphocytes increases after the reduction of the leukocyte count, there is, nevertheless, a reduction of the absolute count to approximately one-tenth of the original number of cells. The relative percentage of large mononuclears increases after treatment, but some of these are, without doubt, myeloblasts.

Reactions Following the Use of Radium. The immediate reactions of radium treatment in the series have been infrequent and mild. Large doses have not been used, and in most instances the series of exposures has been of short duration. Only once did vomiting occur, and it was not severe. In 6 instances there was more or less complaint of nausea with weakness; in 2 there was headache, and in 1 there was quite a persistent complaint of backache.

Radium is a powerful element, and it is necessary to study carefully the results of treatment in order to avoid over-exposure and possible harm. Repeated applications of radium once a week for several weeks may initiate a severe anemia with leukopenia. If the red blood cells fall below 2,500,000, transfusion should be considered and radium treatment temporarily discontinued. When there is reduction of the spleen and reduction of the leukocytes, one's enthusiasm may lead to over-application. As a rule, we have been content to have the leukocytes fall to 20,000 or 15,000 cells. With a definite leukopenia, there seems to be much more likelihood of the occurrence of a crisis with severe anemia and hemorrhage. The anemia may then simulate the primary type, with normoblasts and megaloblasts present. We have noted a temporarily increased fragility of the red blood cells shortly after radium exposure. It is also probable that there is a reduction of platelets after excessive radium treatment. We have learned quite definitely the necessity for the timely use of transfusions in connection with radium treatment. In general, as patients with leukemia approach a serious condition, severe anemia develops. If this anemia can be combated by means of transfusion, life may frequently be prolonged.

Improvement in the General Condition. The improvement in the general condition in some instances is nothing short of remarkable, even after one or two series of exposures. The appetite returns, the toxemia becomes ameliorated, and the strength rapidly increases. The improvement in the general condition does not seem to be the result of a rapid improvement of the anemia, but is probably due to a reduction of the toxemia and leukocytosis and an increase of appetite. Very marked improvement of the general condition is frequently seen with only slight

improvement of the hemoglobin and red cell count. A gain in weight results, in spite of the rapid reduction in the size of the spleen. A certain degree of improvement occurred in all the 30 patients treated. In 26 there was marked improvement, and in 13 of these, a very remarkable improvement.

Cases in Which the Anemia was Not Improved. There were 5 patients in whom, at one time or another during the course of the radium treatment, a definite improvement in the hemoglobin and in the red blood cells did not occur. Three of the 5 were in extremely bad condition. One was so ill that after one treatment radium was discontinued. Another was a severe bleeder and was very resistant to treatment, although the bleeding finally ceased and general improvement occurred without transfusion. The third responded fairly well to a first series of exposures, but returned in a few weeks with severe anemia and ascites. The remaining 2 of the 5 patients with severe anemia were examples of the results of long-continued exposures. Leukopenia and severe anemia, together with a petechial eruption and epistaxis, developed. Transfusions were resorted to, and the patients are both now in very good general condition.

Hemorrhage. The effect of radium exposures on hemorrhage in myelocytic leukemia is important. It can be definitely stated that hemorrhages have very promptly ceased after improvement has been initiated by means of radium. Fourteen patients gave a previous history of hemorrhage. In many instances bleeding had followed the extraction of a tooth. Epistaxis was a more common form of spontaneous hemorrhage. Purpura, petechiae and melena also occurred. In only two instances did hemorrhage follow radium treatment when it had not occurred previously. In all of the other hemorrhagic cases the hemorrhage ceased after the first, second or third exposures. One patient, who was a very severe bleeder, ceased to bleed after two series of exposures. Two patients who bled only after radium treatment had developed a severe anemia and a leukopenia, and hemorrhages were slight; in one instance epistaxis, and in the other petechiae over the legs. Transfusions were immediately resorted to, with satisfactory results.

SUMMARY

1. Thirty consecutive cases of myelocytic leukemia were treated by means of the surface application of radium element over the enlarged spleen. A dosage of 50 and 100 mg. was used. The protection finally adopted was 2 mm. of lead and ½ inch of wood. The splenic area was mapped out into squares after the manner described by Ordway, and the radium was applied over each square for from two to four hours, with a total exposure, usually of twenty-four or thirty-six hours. The exposures were repeated every week until a satisfactory remission was obtained.

2. A certain degree of general improvement, together with reduction of the size of the spleen and of the leukocytic count, occurred in every instance, even in the most advanced and toxic cases. Marked temporary improvement occurred in 26 patients, and a remarkable improvement in 13. It is impossible satisfactorily to discuss the subsequent histories of these cases at this time.

3. Hemorrhage ceased as a rule after one or two series of exposures. In two instances, hemorrhage occurred after radium exposures when it had not occurred previous to treatment. In these instances the hemorrhage seemed to be the result of over-exposure; an anemia also

developed, both the hemorrhage and the anemia were successfully combated by means of transfusion.

4. In 25 patients there was definite improvement of the anemia concomitant with the improvement of the general condition. The reduction of the number of leukocytes was due chiefly to not only an absolute but also a striking relative fall in the myelocytes; there was a striking fall in the absolute count of polynuclears, while their relative percentage remained approximately the same. There was also a marked fall in the absolute count of small lymphocytes.

5. Surface exposures of radium over the spleen of myelocytic leukemia usually effect a very rapid reduction of the size of the spleen, a fall of the leukocyte count, improvement in the general condition and, together with transfusion, constitute at present the most effective temporary measure in the treatment of the disease.

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TUMORS OF THE BLADDER AND THEIR NON-OPERATIVE TREATMENT*

W. F. Braasch, M. D., Rochester, Minn.

When the method of removing bladder-tumors through the cystoscope by means of a high frequency current was first introduced by Beer, it was believed that a method had been discovered whereby all such tumors could be effectively cured. It gradually became apparent, however, that certain types of bladder-tumor could be readily removed by this method while others were affected but little by it. It is now recognized that fulguration is applicable only to tumors of the papillomatous type.

The exact pathological status of a papillomatous tumor of the bladder may be difficult to establish definitely. All papillomas are potentially malignant. Clinically, however, the grade of malignancy varies widely. It is generally recognized that such growths as are characterized by a uniform arrangement of cells and staining qualities, and are well confined within the basement membrane, are of relatively benign type. Nevertheless such tumors, when removed, frequently recur and may later change to a more malignant form. It has also been established that papillomatous tumors with an irregular arrangement of cells and staining qualities, and such as infiltrate the tissues beyond the basement membrane, are distinctly malignant in type, and when removed have a tendency to rapidly recur and metastasize. Between these two extremes of papillomatous tumors, various grades of irregularity in formation and staining qualities of cells may be observed, and it may be difficult, from the pathologic picture, to determine the future clinical course. It is,

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however, often difficult to ascertain the exact microscopic character of a papillomatous tumor from specimens removed through the cystoscope, since the outline, staining qualities, and arrangement of cells, may vary in different portions of the tumor.

As a rule, a satisfactory diagnosis of the nature of a papillomatous tumor can be made by its gross appearance as seen through the cystoscope, together with clinical data. The cystoscopic data which differentiate the malignant from the relatively benign papillomatous tumor are:

1. A tendency to necrosis* and incrustation of the superficial portions, giving it a dirty gray appearance.

2. A heavy, meaty appearance with a thick pedicle, in contrast to the frail structure of a benign papilloma.

3. The frequent presence of an intractable and very irritating cystitis.

Valuable data may be obtained by simple rectal and vaginal palpation which should be done in every case of suspected tumor of the bladder. A malignant tumor involving the base of the bladder will frequently cause palpable thickening of the bladder-wall. When the process has progressed so as to cause a firm, nodular change in the adherent tissues, any operative procedure is useless. It is obvious that no benign tumor could cause such infiltration, and when the latter is present, fulguration would be futile.

It has been found that papillomatous tumors, regarded as relatively benign on microscopic examination, are readily removed by fulguration through the cystoscope, while tumors regarded as frankly malignant on microscopic examination will not react to fulguration. Such tumors as fall in between these two groups may or may not react to fulguration. In the group of papillomatous tumors, when any toubt may exist as to their malignancy, the best method to ascertain the degree of malignancy is through their reaction to fulguration. If a tumor does not respond to three or four such treatments it may readily be concluded that it is of the malignant type and that suprapubic resection should be done without delay.

Several patients have come under our observation in the past few years who had previously been subjected to repeated fulgurations—in the case of one as high as twenty—without affecting the bladder-tumor. This is particularly unfortunate, since a tumor originally amenable to operation may become inoperable after the long delay and ineffectual treatment.

Now that the type of tumor which may be destroyed by fulguration has been definitely established, the question arises: How permanent are the results of the removal of tumors by means of this method? On reviewing our records we find that there were 80 cases of bladder-tumor fulgurated at the Mayo Clinic between January 1, 1911 and September 1, 1917. Of this number 50 were relatively benign papilloma, 0 were papilloma of questionable malignancy, 13 were carcinoma, 1 was angioma, and 7 were questionable papilloma. The Oudin current was employed in the earlier cases but more recently the D'Arsonval current has been used, because of its more rapid results.

Of the 50 patients with benign tumor treated, 33 have been re-examined. No evidence of recurrence was noted in 24 patients, who were examined three or more months following fulguration, while 9 had recurrences. Of the 24 patients having no recurrence, the period follow-

*Albarran, J. Les tumeurs de la vessie. Paris, Steinheil, 1892, 191 p.

ing the initial treatment was as follows: 2, six years; 2, four years; 1, two and one-half years; 2, two years; 2, one and one-half years; 3, one year; and 12, less than one year. This leaves 24 of 33 patients (73 per cent) with benign papilloma who have been re-examined, without any evidence of recurrence. It is probable that this percentage will be reduced by subsequent recurrence among the patients treated within the last year or two. Of the 9 patients with recurrence there were four who had a recurrence of the tumor following the first fulguration, but who on recent examination were found well, over periods of from 1 to 4 years. In the 5 patients showing a recurrence at the time of the last examination, the interval following fulguration was as follows: 2, four months; 1, six months; 1, six months, and subsequently eight months; and 1 has had three yearly recurrences.

The site of recurrence was found at the original site of the primary tumor in 6 cases, and at different sites in 3. The exact time of recurrence was difficult to ascertain because of the irregularity of examination following fulguration. However, of the 9 patients with recurrence it was noted in 8 in less than six months. In the one patient in whom the recurrence was repeated it was observed one and one-half years following fulguration. No recurrences were noted in cases in which the primary tumor was removed by one or two fulgurations. This is corroboratory of a previous observation that the degree of malignancy is in direct proportion to the number of fulgurations necessary to its removal. Keyes claims that recurrence will usually take place within three months. Of the 3 patients with primary multiple tumors re-examined, 2 had multiple recurrences, which would corroborate Keyes' statement that recurrences following the fulguration of multiple tumors are multiple. Multiple recurrence was also noted in one patient with primary single tumor. A second recurrence was observed in but two patients and the primary tumor was multiple in both. Repeated recurrences usually occur with multiple primary tumors.

Of the remaining 17 patients who were not re-examined, 5 were reported as symptomatically well, and no subsequent data were available from 12. Of the patients reported well, the period following the last treatment was as follows: 1, six and one-half years; 1, six years; 1, five years; 1, two and one-half years; 1, two years. Of the 12 patients without subsequent report, 8 were fulgurated within the past year. While it is difficult to draw exact conclusions as to recurrences from this group without having made a cystoscopic re-examination, nevertheless it is significant that 5 patients are reported alive and well from two to six years after fulguration. It is also of interest that there remain but 4 patients who have not been heard from. It is fair to assume that the majority of these are still living.

Of the 9 patients with papilloma of doubtful malignancy, 4 were fulgurated without success and, later, resection was done. Of the remaining 5, 1 was well two years, and 1 six months afterward, 1 had multiple recurrences annually, 1 showed extensive recurrence five months later, and 1 was treated three months previously. An interesting occurrence was that of two tumors in the same bladder; one was relatively benign and was readily removed by fulguration; the other was not affected by fulguration and on resection later, was found to be malignant. It is evident that although a few cases of malignant papilloma will respond to fulguration, the majority will not.

Of the 13 patients with carcinoma, in 9 the treatment was given for recurrences following suprapubic resection for carcinoma. In 4 patients

the tumors were of a doubtful nature on clinical examination, but did not respond readily to fulguration and were operated on later. Of the 9 patients that were fulgurated following operation, 1 was fulgurated after fifteen months and has been well for two years, 1 was fulgurated after two years and has been well four years, 1 was fulgurated after eighteen months, and in a letter from the patient three years later he states that he is well, 1 was fulgurated after three years and has not been seen for three months, 1 has been fulgurated yearly for the past three years for recurrences and was last examined five months ago, and 1 was fulgurated three months after operation and has not been examined for three months. Three of the patients have died from one to two years after operation. It will be noted that the period of freedom from recurrence was much longer after fulguration than after operation. The time of recurrence following fulguration was more than a year in all but two patients, and much longer than that observed with relatively benign papilloma. Tumors which have been frankly malignant at operation will frequently respond to fulguration when they recur. The degree of malignancy is evidently reduced with successive recurrence, and even though the patient may not be cured, life is unquestionably prolonged.

In the 9 cases of recurrence in this group, 5 were at the previous site of the tumor and 4 were at different sites. In 3 cases the recurrence was multiple, and in 3 single. Cystoscopic examination several months after resection for a malignant tumor will occasionally reveal evident proliferation of the mucosa at the site of the previous incision. There may be no evidence of other involvement of the external wound, but this proliferation may persist and remain stationary for many months. It is advisable, however, to give it a thorough course of fulguration and radium exposure.

In the 7 cases of questionable papilloma, the time since the last fulguration is as follows: 1, six years; 1, five years; 1, four years; 1, three years; 2, one and one-half years; and 1, less than a year. None of these patients have been re-examined, but letters received from them indicate that there is no recurrence.

Papillomatous proliferation of the mucosa to a slight degree, the exact nature of which it is difficult to determine, is sometimes visible in the bladder. Such tumors are found more often near the ureteral meatuses or the internal vesical sphincter, and although they are probably the result of a slight chronic inflammatory reaction of the mucosa, no other evidence of inflammation may be visible. They may disappear spontaneously but they will occasionally remain stationary in size for a period of several years. It is quite possible that some of these are the forerunners of papillomas or malignant tumors, which is further suggested by the frequency with which malignant tumors are found near the ureteral meatuses. Such tumors when discovered should be removed at once by fulguration.

Severe chronic inflammation will occasionally cause such extensive proliferation of the mucosa that it may simulate a true bladder-tumor. This is particularly true with vesical tuberculosis. Microscopic examination of the tissue in question, or catheterization of the kidneys, would usually identify the lesion. The specimen obtained, however, may be unsatisfactory and renal catheterization may be impossible, thus making identification of the tumor exceedingly difficult.

The number of treatments necessary to remove tumors is not always in ratio to their size. Occasionally, tumors of considerable size are removed in one fulguration, whereas much smaller ones may require sev-

eral treatments. It would seem that the rapidity with which the tumors disappear is in a measure in proportion to the degree of malignancy. The treatment of large tumors may be hastened by the preliminary removal of much of the tissue by means of a snare as suggested by Buerger.

Following the removal of a papilloma by fulguration there will usually be considerable inflammatory reaction in the mucosa, and consequent edema and granulation tissue may simulate a persistent remnant of the papilloma. This, however, will gradually disappear spontaneously in the course of three or four weeks. Occasionally, the bladder-mucosa at the site of the suprapubic incision remains congested and irregularly infiltrated for a long time following fulguration, and such congestion when persistent is frequently indicative of underlying malignancy. Thorough fulguration of the area should be tried, and if the congestion still remains radium should be used.

Radium. Since radium has been used with such good results in treating superficial malignant conditions, such as in the skin, larynx, etc., it would be reasonable to expect similar results in the bladder. Thus far, however, the experiences reported have not been encouraging. Geraghty believes that it is of little or no value in the treatment of frankly malignant tumors of the bladder. His method of application consisted of hourly exposures with 100 mg. of radium, screened by a brass capsule of 3 m. m. in thickness, which is applied directly over the tumor by rigid instruments within the bladder. He reports a series of papillomatous tumors, however, that did not respond to fulguration until they had been exposed to radium. After this they were readily removed by fulguration. Barringer, on the other hand, reported evident cures with radium alone in 3 of 9 cases of inoperable malignant tumors. His technic differs from that of Geraghty in that the unshielded original lead capsule of radium is inserted in the bladder and the patient placed in a position to bring the capsule in contact with the tumor. It is further allowed to remain in the bladder for a much longer time, namely, five or six hours. Kolischer* reported successful removal of several malignant tumors with the use of mesothorium. He employs this intravesically, leaving the capsule in the bladder as long as 24 hours.

Our experience with radium has been largely as an aid to post-operative and preoperative treatment. Following resection of malignant tumors, it has been our custom to leave the unshielded radium capsule in the bladder for several hours in the hope of destroying any superficial malignant cells remaining. In preoperative and inoperable conditions it has been found valuable in reducing infection and cleaning up foul-smelling urine. In cases of persistent bleeding from the tumor a few hours of exposure to radium will often control it. This, together with deep x-ray exposure, is occasionally of value in controlling pain sometimes found in inoperable cases. In two cases in which there was secondary recurrence of papillary carcinoma, the tumor disappeared following long intravesical application of 100 mg. of radium. In 3 cases of secondary recurrence of the tumor in the suprapubic wound following resection, the nodules were softened and to all appearances the process was temporarily controlled. It may be said, therefore, that although radium does not have the brilliant therapeutic results of fulguration in the treatment of bladder-tumors, it is, nevertheless, a valuable adjunct when the condition is malignant.

*Kolischer—Rad otherapy and diathermy in malignant tumors of the bladder. Urol. and Cutaneous Rev., 1916, XX, 66-67.

In summarizing our experiences with the non-operative treatment of tumors of the bladder, it may be said:

1. Fulguration offers a safe and comparatively easy method of removing bladder papillomas.

2. Fulguration is applicable only to the papillomatous tumors of a relatively benign type.

3. Although the ultimate results following fulguration are much superior to those following suprapubic resection, the method does not always offer a permanent cure.

4. The degree of malignancy is usually readily ascertained by the cystoscopic appearance and clinical data.

5. In doubtful cases the degree of malignancy is best ascertained by its reaction to fulguration.

6. The percentage of recurrence of papillomas in a series of 33 cases repeatedly re-examined was 27.

7. Recurrence when present usually occurs within six months after fulguration and is generally at the site of the primary tumor.

8. Multiple recurrence is more often observed with multiple primary tumors.

9. Tumors which have been frankly malignant at operation will frequently respond to fulguration when they recur.

10. The degree of malignancy is evidently reduced by successive recurrences.

11. Small papillomas, usually situated near ureteral meatuses, are occasionally accidentally discovered. While some are inflammatory, others are forerunners of large papillomas and should be fulgurated.

12. Radium is of value (1) as a prophylactic measure following surgical resection of bladder-tumors, (2) to control hematuria and pain, (3) occasionally in removal of malignant tumors, particularly when recurring.

REVIEWS AND ABSTRACTS

Isaac Levin, M. D., (New York. X-Ray and Radium Treatment of Leukemia and Hodgkin's Disease. Medicine and Surgery. I, 144-416. June 1917.

"It has been proved experimentally on normal animals that the blood, the spleen, the bone-marrow and the lymph-nodes are the most sensitive organs in the body to the action of radium and x-rays. A few hours after the radiation of a normal animal there is noticed destruction of the cells of the lymphoid tissue, the spleen and the bone-marrow. The readiness with which the cells react to the rays differs in the various types of cells. In the bone-marrow, for instance, the most easily affected are the lymphocytes and the non-granulated myelocytes. The eosinophiles and the mast cells are less readily affected. The longest remain intact,—the neutrophile polymorphonuclear cells. The red-blood cells are quite resistant to the action of the rays. A certain time, after the cessation of the raying, the blood-forming organs recover their normal state."

"The destructive action of radium and x-ray on the leucocytes of the blood and on the blood-forming organs is by far more pronounced in the leukemic organism, than in the organism of a normal animal. The

amount of destruction of leucocytes in the blood of a leukemic is perfectly astounding. Cases are reported in which during six weeks' treatment the white blood count went down from 1,250,000 to 8,000. Occasionally this fall in the number of leucocytes is preceded by a short period of a slight rise of the number of leucocytes. At the same time with the fall in the number of leucocytes there takes place a qualitative change in the morphology of the blood. The myelocytes which are very abundant in the splenic myelogenous form are most readily destroyed and replaced by riper forms. The following chart-form, a case of myelogenous leukemia treated by the writer, illustrates the condition:—

	Poly.	Lymp.	Myelo.	Trans.	Eosin.
Before x-ray	42	6	49	1	2
After x-ray	72	1	23	..	1

"In lymphatic leukemia there takes place a more uniform destruction of the leucocytes without marked qualitative changes. The swelling of the spleen and of the lymph-glands is promptly reduced by the action of the x-ray and radium. Cases which came to autopsy showed also an entensive destruction of the leucocytes of the bone-marrow. The latter appeared red on gross inspection and consisted mainly of erythrocytes. The mechanism of the action of the rays on the leukemic blood and blood-forming organs consists in the destruction of young, unripe leucocytes (myelocytes) in the circulating blood, spleen-marrow and lymph-glands. The mechanism of this action is quite similar to the action of the rays on malignant tumors. In either case the etiology of the disease is unknown, but the pathogenesis and the clinical manifestations are due to unlimited proliferation of groups of abnormal cells in certain localities. In leukemia the locus of the formation of these abnormal cells is the spleen, the marrow and the lymph-glands. The writer has shown in previous publications that carcinoma or sarcoma under the influence of radium or x-ray may be replaced by dense connective-tissue. It is possible that when treatment is begun early and kept up for a sufficient length of time, the spleen, marrow and lymph-glands may be so changed that the over-production of unripe forms of leucocytes may be permanently inhibited and this irrespective of whether the rays produce any effect on the unknown etiological factor of the disease. The initial increase in the number of leucocytes in the circulating blood is probably due to a temporarily increased migration of the cells from the spleen, bone-marrow and the lymph-glands."

"Methods and Clinical Results. *Myelogenous Leukemia.*—The first reports of favorable results of x-ray therapy of the disease were published fifteen years ago. Since then a great number of cases were treated with excellent results, and the fact is firmly established that x-ray therapy is a specific method of treatment and is capable of prolonging life in every case of this heretofore hopeless disease. Even when the general condition of the patient is extremely bad, he may promptly rally under treatment. At the beginning of the treatment, there may take place an apparent exacerbation of the clinical symptoms,—headache, nausea, vomiting, diarrhea and rise of temperature. But all these symptoms soon subside and are followed by a marked improvement of the general condition, an increase of strength and body weight. All the clinical symptoms accompanying the disease, as for instance, cessation of menstruation, priapismus, hemorrhagic diatheses and fever, promptly disappear.

Later the blood-picture improves and the spleen diminishes in size. Thus a complete clinical remission of the disease sets in which lasts a longer or shorter period of time, but is then followed by a relapse, which may be again influenced by x-ray therapy. Ultimately the periods of remission become shorter and the patient succumbs to the disease."

"There cannot be any doubt left that the life of the patient may be prolonged for a number of years under the influence of this treatment. It is impossible to assert at present whether a complete cure of the disease will be attained ultimately, when the treatment is begun early and the technique of it is improved, but the results so far are remarkable, indeed. The technique of x-ray therapy employed in these cases is similar to the one employed by the writer in treating cancer cases."

"The Coolidge tube is used exclusively. The distance between the target and the skin is 8 inches, and the length of the spark is 8½ inches. A Bauer penetrometer, an apparatus which measures the hardness of the rays, as well as the milliamperemeter are placed so that they can both be observed constantly through the lead glass window. The penetration or hardness of the rays, kept at 10 Bauer, and 5 milliamperes are sent through the tube. Each field of the skin represents a circle of from 1 to 2 inches in diameter, depending upon the region treated. The regions treated are the spleen, the shafts of the long bones, the sterum, the chest-wall and the liver. A number of fields are mapped out and 4 fields are treated at every sitting The treatments are given three times a week for about six weeks. At the beginning, until the tolerance of the patient is ascertained, daily 10x are given to each field, subsequently the dose is increased to 20x per field. The treatment is constantly controlled by blood examination. At the beginning it is well to take a blood-smear before and after each treatment, subsequently one weekly examination of the blood is done. As soon as the blood-picture is sufficiently improved, the treatment is interrupted, which usually takes place in about six weeks. The time for the beginning of the next course of treatment depends upon the condition of the patient."

"*Lymphatic Leukemia.*—This group of cases does not respond to the x-ray treatment quite as readily as the myelogenic type, but in the majority of cases the condition subsides, and the life of the patient is prolonged. The method of treatment is identical with the one employed in the myelogenous form, only a great deal of care must be taken in the treatment of the enlarged lymph-glands. For the latter tissue the writer found that radium acts more promptly than the x-rays. A combined treatment with both agents should therefore be employed in cases of lympathic leukemia."

"*Hodgkin's disease,* as stated above, resembles leukemia in many respects, only usually with less prominent involvement of the spleen and no increase in the number of leucocytes in the blood. The affected lymph-glands diminish very rapidly in size under x-ray and more readily under radium treatment, and with it there is a marked improvement in the general condition of the patient. The methods of treatment are identical with those employed in the treatment of lymphatic leukemia and should continue for months. The size of the glands diminishes to a certain extent; they remain stationary. Should the treatment be interrupted for a time, then at the first evidence of a new enlargement of the glands the treatment must be repeated. The opinion prevails that the action of the radiations are only palliative and that ultimately the patients fail to respond to treatment. These unsatisfactory results are most probably due

to the fact that x-ray treatment is attempted only late in the course of the disease and is not pursued with sufficient energy. In a few early cases, the writer succeeded in arresting the disease for a number of years."

"*Splenic pseudo-leukemia* gives identical clinical results and requires the same technique as the cases of lymphatic leukemia."

"*Mediastinal tumors* present usually lymphomata of the mediastinal lymph-glands. The disease usually begins to give clinical symptoms only in its advanced stage, and therefore the results of the treatment are temporary; nevertheless, a number of cases were reported in which x-ray plates taken before and after treatment showed a marked diminution of the size of the tumor which was accompanied by improvement in the general clinical symptoms. The writer recently reported such a case. In order to obtain the early cases of mediastinal tumors it is necessary to do a fluoroscopic examination of the chest of all early cases of Hodgkin's disease at frequent intervals. Wherever an enlargement of the mediastinal glands is noted, an immediate energetic raying of the chest should be undertaken."

"*Lymphosarcoma* always presents a malignant degeneration of a lymph-gland which was previously in a state of hyperplasia—a lymphoma. Lymphosarcoma is consequently a late stage of Hodgkin's disease. It must therefore be expected *a priori* that the results of x-ray and radium treatment of these cases can only be palliative. Still the writer succeeded recently in keeping in check for a year and a half a far-advanced case of mediastinal tumor which invaded and completely destroyed the sternum. In another case of lymphosarcoma in which death was caused ultimately by involvement of the whole peritoneum, the cervical glands completely disappeared under radium treatment. Another tumor in the same patient developed in the nasopharynx, completely obstructed the nasal respiration and deglutition, and interfered greatly with the rest of the patient. A tube of radium was introduced into the nasopharynx by the aid of a Belloc tube and left there for two hours. The tumor disappeared completely and the patient became comfortable."

"As stated above, other diseases of the hemopoietic system—anemias and splenomegalies of different origin—do not respond to radiations."

"Leukemia and Hodgkin's disease present the most hopeless conditions in the whole domain of medicine, and the results of the x-ray and radium treatment are extremely encouraging and should be employed in every case as soon as the diagnosis is made. Moreover, the treatment must be conducted with great energy; half measures are less than useless."

* * * * *

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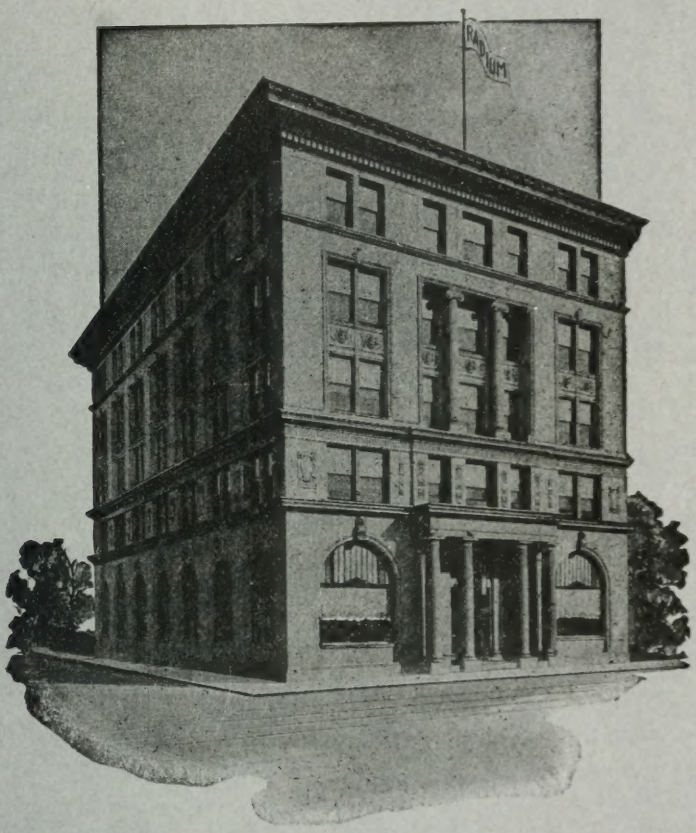

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